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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/988,013
Filing Date: November 16, 2001
Appellant(s): LEUNG ET AL.

Barbara A. McDowell
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 31 March 2008 appealing from the Office action mailed 30 August 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

GORMAN, S. D. "Reshaping a Therapeutic CD4 Antibody", Proc. Natl. Acad. Sci. USA, vol. 88, no. (May 1991), pp. 4181-4185.

5,789,554 LEUNG et al 8-1998

LEUNG, S-O. "Construction and Characterization of a Humanized, Internalizing, B-Cell (CD22)-Specific, leukemia/Lymphoma Antibody, LL2", Molecular Immunology, vol. 32, no.17/18 (1995), pp. 1413-1427.

(9)(a) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 28-32 and 38-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

As presently amended the claims are drawn to a method of designing the amino acid sequences of the variable domains of a humanized monoclonal antibody comprising comparing the amino acid sequences of the light chain and heavy chain variable domains of a monoclonal antibody to be humanized with the light and heavy chain variable domains of human antibodies, selecting frameworks from a first human antibody for the light chain and from a second and third human antibodies for the heavy chain wherein the heavy chain FR1, FR2 and FR3 are selected from the second human antibody and FR4 is selected from the third human antibody and incorporating the framework sequences with the corresponding light an heavy chain CDRs of the monoclonal antibody to be humanized to design humanized light and heavy chain variable domain amino acid sequences, wherein FR4 is selected from the human NEWM antibody, or wherein the light chain framework regions are selected from the human REI antibody, or the heavy chain FR1, FR2 and FR3 are selected from the human EU antibody as well as a method for producing the designed humanized antibody in host cells. Thus, the claims are drawn to a method of designing and producing a subgenus of humanized antibodies that comprise just any CDRs, or comprising the heavy chain FR4 sequence of the human NEWM antibody, or comprising the light chain frameworks of human REI, or comprising the heavy chain FR1, FR2 and FR3 from the human EU antibody. The specification as filed only discloses a single monoclonal antibody LL2, which was humanized according to the claimed method in which the LL2 CDRs of the light chain were grafted onto human REI frameworks and the heavy chain CDRs were grafted onto the human EU frameworks, except for FR4, which was from the human NEWM antibody. Applicant's reliance on a

single disclosed species is insufficient to support the broader scope of the claims encompassing multiple subgenera because there is insufficient disclosure of a "representative number of species" and there is substantial variation within the subgenera claimed. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what does not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) ("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). For example, according to Gorman et al (Proc. Natl. Acad. Sci, USA, 88:4181-4185, May 1991) the largest unknown variable when reshaping an antibody is the selection of the human immunoglobulin variable region from which the framework sequences are derived because the framework regions hold the CDRs in their correct spatial orientation and can sometimes even participate in antigen binding. At present, there are insufficient published reshaping results to generalize a “best framework” selection strategy (Gorman et al, at pg. 4182, 2nd col.). There is no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other CDRs other than the LL2 are suitable for grafting onto the human REI light chain frameworks and onto the human EU and NEWM heavy chain frameworks. Further, in contrast to the

scope of the claims, Applicant's disclose that the human frameworks are selected based on the highest degree of sequence homology to the murine variable region sequences. While there may be a general method of selecting the most homologous frameworks for humanizing a given monoclonal antibody, applicants' priority documents only provide adequate written support for the humanization of murine monoclonal antibody LL2 wherein the light chain frameworks are from the human REI antibody and the heavy chain frameworks for FR1-FR3 are from the human EU antibody and heavy chain FR4 is from the human NEWM antibody. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith* 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05. One of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the multiple subgenera of the claimed method in view of the single disclosed species.

Therefore, the instant claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the instant claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in the instant claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

(10)(a) Response to Argument

Appellant reviews the case law cited by the examiner in the above rejection. The examiner maintains that the case law is relevant and consistent with the instant rejection for lack of adequate written support. Appellant states that the instant claims are distinguished from the cited case law in that the instant claims are drawn to a method and not a product. Appellants' arguments have been fully considered but are not found persuasive because it is irrelevant that the present claims are drawn to a method, the statute applies to all types of inventions. *Rochester* also attempts to

distinguish *Fiers*, *Lilly*, and *Enzo* by suggesting that the holdings in those cases were limited to composition of matter claims, whereas the '850 patent is directed to a method. We agree with the district court that that is "a semantic distinction without a difference." *Univ. of Rochester*, 249 F. Supp. 2d at 228. Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

Appellant argues that the original specification clearly informs a person of ordinary skill in the art that Appellant possessed a method for humanizing antibodies in which each variable region framework (FR) sequence of a non-human antibody is compared to a corresponding variable region framework (FR) sequence of a human antibody to determine the degree of sequence homology between the non-human antibody FRs and the human antibody FRs, and then each FR in the non-human antibody is replaced with a human antibody FR which exhibits sequence homology to the non-human antibody FRs and Appellant points to the following disclosure in the specification (pp. 21-22):

> By comparing the murine variable (V) region framework (FR) sequences of LL2 to that of human antibodies in the Kabat database (Kabat *et al.,* Sequences of Proteins of Immunological Interest, 5th ed., U.S. Department of Health and Human Services, U.S. Government Printing Office, Washington, D.C.), which is incorporated by reference, the human REI (FIG. 1A, SEQ ID NO. 6) and EU (FIG. 1B, SEQ ID NOS. 9 and 8) sequences were found to exhibit the highest degree of sequence homology to the FRs of VK and VH domains of LL2, respectively. Therefore, the REI and EU FRs were selected as the human frameworks onto which the CDRs for LL2 VK and VH were grafted, respectively. The FR4 sequence of NEWM, however, rather than that of EU, was used to replace the EU FR4 sequence for the humanization of LL2 heavy chain. Based on the results of computer modeling studies (FIGS. 2A and 2B), murine FR residues having potential CDR contacts, which might affect the affinity and specificity of the resultant antibody, were retained in the design of the humanized FR sequences (FIG. 1).

Based on the disclosure, Appellant concludes that it is clear that each variable region framework sequence was compared to its corresponding framework region in a database of human antibodies and that replacement of framework regions was based on sequence homology. According to Appellant, this is the invention claimed in the present application and the specification shows that Appellants were in possession of this invention as of their earliest filing date. Appellants' arguments have been fully considered but are not found persuasive. It is reiterated that the specification as filed only discloses a method of humanizing a single monoclonal antibody, murine monoclonal antibody LL2, which was humanized according to the claimed method in which the LL2 CDRs of the light chain were grafted onto human REI frameworks and the heavy chain CDRs were grafted onto the human EU frameworks, except for FR4, which was from the human NEWM antibody and wherein the REI, EU and NEWM human frameworks were selected based on high sequence homology to the LL2 frameworks as noted by Appellant. Appellant again attempts to distinguish claims to humanized antibodies (e.g., product claims) from methods of designing humanized antibodies (e.g., method of making), however, as discussed supra, the district court makes clear that the statute applies to all types of inventions. To the extent that Appellant is asserting that the examiner's arguments are not on point, the examiner maintains that regardless of whether the claims are directed towards a subgenus of humanized antibodies (i.e., those comprising human REI, EU and NEWM frameworks) or to a method of designing a subgenus of humanized antibodies (i.e., designed using human REI, EU and NEWM frameworks), the issue on appeal for lack of adequate written support is the same. The selection of particular human heavy (e.g., EU for FR1-3 and NEWM for FR4) and human light chain framework sequences (e.g., REI) based on homology to the corresponding framework sequences of murine monoclonal antibody LL2 does not adequately convey possession of the presently claimed method of designing the broader subgenus of humanized antibodies. The instantly claimed method requires the human REI light chain frameworks and human EU heavy chain frameworks, except for FR4, which is from the human NEWM antibody, and thus, encompasses incorporating the CDRs of any antibody into these human frameworks,

irrespective of sequence homology. The specification does not disclose the selection of the particular combination of human REI, EU and NEWM frameworks in the design and humanization of any other antibody other than murine monoclonal antibody LL2. Appellant's reliance on a single disclosed species is insufficient to support the broader scope of the claims encompassing multiple subgenera because there is insufficient disclosure of a "representative number of species" and there is substantial variation within the subgenera claimed. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) ("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). For example, according to Gorman et al (Proc. Natl. Acad. Sci, USA, 88:4181-4185, May 1991, cited on PTO-892 mailed 2/20/2007) the largest unknown variable when reshaping an antibody is the selection of the human immunoglobulin variable region from which the framework sequences are derived because the framework regions hold the CDRs in their correct spatial orientation and can sometimes even participate in antigen binding. At present, there are insufficient published reshaping results to generalize a "best framework" selection strategy (Gorman et al., pg. 4182, 2nd col.). There is no evidence in the disclosure showing applicant conveyed or contemplated that any other CDRs other than the LL2 CDRs are suitable for grafting onto the human REI light chain frameworks and onto the human EU and NEWM heavy chain frameworks. Further, in contrast to the scope of the claims, Appellant's disclose that the human frameworks are selected based on the highest degree of sequence homology to the

murine LL2 variable region sequences, not that the CDRs of just any monoclonal antibody are suitable for incorporation into the REI light chain framework sequences and into the EU and NEWM heavy chain framework sequences as presently required by the claims. For example, different non-human (e.g., murine) antibodies contain different heavy and light chain sequences and thus, for any particular non-human antibody, the selection of human frameworks having the highest homology with the corresponding frameworks of the non-human antibody being humanized as set forth in the specification would have led the skilled artisan to the selection of the most homologous human frameworks for that particular non-human antibody, not necessarily to the human REI light chain frameworks and the human EU and NEWM heavy chain frameworks. As illustrated in the table provided by Appellant at pg. 12 of the Brief humanizing different antibodies by selecting the most homologous human frameworks leads to the selection of different human frameworks. While there may be a general method of selecting the most homologous frameworks for humanizing a given monoclonal antibody, the instant disclosure as well as Appellants' priority documents only provide adequate written support for the humanization of murine monoclonal antibody LL2 wherein the selected light chain frameworks are from the human REI antibody and the selected heavy chain frameworks for FR1-FR3 are from the human EU antibody and heavy chain FR4 is from the human NEWM antibody based on high homology to the corresponding frameworks regions of the LL2 antibody. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See, e.g., *In re Lukach*, 442 F.2d
967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range) and *In re Smith* 173 USPQ 679, 683 (CCPA 1972). One of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the subgenus of the claimed method in view of the single disclosed species.

At pg. 11 of the Brief, Appellant refers to the examiners comment in the advisory action mailed 1/28/2008, in which the examiner stated:

> the specification does not fully develop the concept that there are universal or best fit human frameworks for humanization in which just any non-human CDRs may be grafted and retain the antigen specificity and affinity of the parental non-human antibody. Further, in light of the prior art, *e.g.,* Gorman *et al,* such a universal property appears to be unpredictable since different antibodies will have different amino acids in the framework which are important for antigen binding and stability.

Appellant acknowledges that they have not argued that there are universal or best fit frameworks which work with any CDRs. Appellant states that the fact that the claimed method requires some experimentation in comparing the frameworks of various human antibodies to the framework regions of the non-human antibody which is to be humanized, and selecting those which provide the "best fit" for particular CDRs in terms of homology does not show that Appellants did not possess the invention. Nor does the fact that application of the method does not lead to selection of the same framework regions for every antibody humanized lead to such a conclusion. Appellant asserts that these are both red herrings. Appellants' arguments have been fully considered but are not found persuasive. The above excerpt which Appellant references from the advisory action is consistent with the scope of the claims and the issue of lack of adequate written support therefore. The claims encompass a method of producing a subgenus of humanized antibodies comprising just any CDRs in the context of human REI light chain frameworks and the human heavy chain EU FR1-3 regions and the human heavy chain NEWM FR4 region (e.g., last three lines of claim 28). Thus, perhaps Appellants should be arguing that there are universal or best fit frameworks which work with any CDRs, given that this is exactly what is being claimed. Further, Appellants arguments regarding comparing and selecting human frameworks which provide the best fit for particular CDRs in terms of homology and that such selection would not lead to the same framework regions for every antibody humanized does not show that appellants did not possess the invention are not on point because as discussed supra, the claims are directed to a method of producing a subgenus of humanized antibodies comprising just any CDRs in the context of human REI light chain frameworks and the human

heavy chain EU FR1-3 regions and the human heavy chain NEWM FR4 region. Thus, rather than attempting to mislead Appellant, the examiner was merely pointing out in the advisory action that the claims do not recite the LL2 CDRs and encompass any CDRs in the context of fixed human frameworks (e.g., REI, EU and NEWM), whereas the written description sets forth that human frameworks exhibiting the highest sequence homology should be selected and murine framework residues which might affect affinity and specificity of the humanized antibody should be retained in the design of the humanized framework sequences. Again, the as filed disclosure does not fully develop the concept that there are universal or best fit human frameworks for humanization in which just any non-human CDRs may be grafted and retain the antigen specificity and affinity of the parental non-human antibody. Further, in light of the prior art, e.g., Gorman et al (supra), such a universal property appears to be unpredictable since different antibodies will have different amino acids in the frameworks which are important for antigen binding and stability, consistent with the written description of the present application.

Appellants' argument that other antibodies have been produced by the presently claimed method and disclosed in different applications and publications (e.g., table at pg. 12 of the Brief) is acknowledged, but is not found persuasive. It is noted that only four of the other ten antibodies in the table at pg. 12 of the Brief contain the human REI light chain frameworks and the human EU and NEWM heavy chain frameworks as presently claimed. Nonetheless, the issue is not whether one skilled in the art could make and use the claimed method for designing humanized antibodies other than the humanized LL2 antibody, the issue is whether the written description of the instant application and the priority documents adequately describes or discloses a method for designing the subgenus of humanized antibodies comprising the human REI light chain frameworks and the human EU (FR1-3) and NEWM (FR4) heavy chain frameworks. As discussed above, the as filed specification only discusses the selection of the human REI light chain frameworks and the human EU and NEWM heavy chain frameworks (based on high homology) for designing and producing the humanized LL2 antibody, and the specification contains no broadening language of any kind. The disclosure does not adequately convey that Appellants' contemplated that any other CDRs other

than the LL2 CDRs are suitable for grafting onto the human REI light chain frameworks and the human EU and NEWM heavy chain frameworks as presently claimed. Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.). An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See MPEP 2161.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991), with respect to the first paragraph of §112 the severability of its "written description" provision from its enablement ("make and use") provision was recognized by this court's predecessor, the Court of Customs and Patent Appeals, as early as *In re Ruschig,* 379 F.2d 990, 154 USPQ 118 (CCPA 1967). Although the appellants in that case had presumed that the rejection appealed from was based on the enablement requirement of §112, *id.* at 995, 154 USPQ at 123, the court disagreed: the question is not whether [one skilled in the art] would be so enabled but whether the specification discloses the compound to him, specifically, *as something appellants actually invented.* ... If [the rejection is] based on section 112, it is on the requirement thereof that "The specification shall contain a written description *of the invention* * * *." (Emphasis ours.) *Id.* at 995-96, 154 USPQ at 123 (first emphasis added). The issue, as the court saw it, was one of fact: "Does the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed]?" *Id.* at

996, 154 USPQ at 123. In a 1971 case again involving chemical subject matter, the court expressly stated that "it is possible for a specification to *enable* the practice of an invention as broadly as it is claimed, and still not *describe* that invention." *In re DiLeone,* 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971) (emphasis added). As an example, the court posited the situation "where the specification discusses *only* compound A and contains *no* broadening language of any kind. This might very well enable one skilled in the art to make and use compounds B and C; yet the class consisting of A, B and C has not been described." *Id.* at 1405 n.1, 168 USPQ 593 n.1 (emphases in original). *See also In re Ahlbrecht,* 435 F.2d 908, 911, 168 USPQ 293, 296 (CCPA 1971) (although disclosure of parent application may have *enabled* production of claimed esters having 2-12 methylene groups, it only *described* esters having 3-12 methylene groups).

At the top of pg. 13 of the Brief, Appellant refers to two US Application publications (US20030040606A1 and US20050033028A1) which Appellant asserts also disclose the production of humanized antibodies by the presently claimed method as do articles by Leung et al (Molecular immunology, 32(17-18):1413-1427, 1995, of record, PTO-892 mailed 2/20/2004) and Leung et al (Hybridoma v13:469-475, 1994, IDS reference 4 filed 2/2/2007). Neither US20030040606A1 nor US20050033028A1 disclose antibody humanization using human REI light chain frameworks and the human heavy chain EU FR1-3 regions and the human heavy chain NEWM FR4 region as required by the presently claimed method. Consistent with the examiners position US20030040606A1 and US20050033028A1 humanize a different murine anti-CD22 antibody, RFB4, wherein the most homologous human frameworks are selected and are not the human REI, EU and NEWM frameworks. Leung et al (Molecular immunology, 32(17-18):1413-1427, 1995), (applied as prior art below, see item nos. (9)(c) and (10)(c)) is the non-patent literature equivalent of the instant disclosure and is limited to designing and producing the humanized LL2 antibody, in which the LL2 CDRs are grafted onto the light chain REI frameworks and the heavy chain EU and NEWM frameworks. Leung et al (Hybridoma v13:469-475 (1994) discloses the production of a chimeric LL2 antibody, not a humanized LL2 antibody. The chimeric LL2 antibody

comprises the murine heavy and light chain variable regions of LL2 combined with human kappa and IgG1 constant region domains. Thus, Appellants' assertion that these documents disclose the production of humanized antibodies *generally* by the presently claimed method is curious given that US20030040606A1 and US20050033028A1 and Leung et al (Hybridoma v13:469-475, 1994, IDS reference 4 filed 2/2/2007) do not disclose antibody humanization using human REI light chain frameworks and the human heavy chain EU FR1-3 regions and the human heavy chain NEWM FR4 region as required by the presently claimed method and Leung et al (Molecular immunology, 32(17-18):1413-1427, 1995, PTO-892 mailed 2/20/2004) is limited to the LL2 antibody. Nevertheless, the issue remains the lack of adequate written support in the instant application, not whether other antibodies have been or could be made according to the claimed method of designing the variable domain sequences of a humanized antibody. "It is not a question whether one skilled in the art might be able to construct the patentee's device from the teachings of the disclosure of the application. Rather, it is a question whether the application necessarily discloses that particular device." *Id.* at 536. *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004).

Therefore, the instant claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the instant claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112.

Priority

The disclosure of the prior-filed application, USSN 08/820,576 with which applicant argues, does not to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for the present claims (see item nos. (9)(a) and (10)(a) above). See e.g., *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971), in which Applicant was not entitled to the benefit of a parent filing date when the claim was

directed to a subgenus (a specified range of molecular weight ratios) where the parent application contained a generic disclosure and a specific example that fell within the recited range because the court held that subgenus range was not described in the parent application.

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

(9)(b) Grounds of Rejection

Claims 28-29 and 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung et al [a] (US Patent 5,789,554, issued 8/4/1998, IDS reference A2 filed 4/30/2002).

Leung et al [a] teach a method of designing the amino acid sequences of the variable domains of a humanized monoclonal antibody comprising comparing the murine variable domain framework sequences of monoclonal antibody LL2 to that of human antibodies in the Kabat database and selecting the human REI (VL) and human EU (VH) frameworks as the frameworks onto which the LL2 CDRs were grafted, however, the FR4 sequence of human NEWM was used in place of the human EU FR4 in the heavy chain (i.e., framework regions form at least three different human antibodies (REI, EU and NEWM) and the heavy chain framework regions are from at least two different human antibodies (EU and NEWM)) and the framework regions of the EU human heavy chain and FR4 of NEWM have at least 62.5% sequence identity with the corresponding framework regions of monoclonal antibody LL2 and the framework regions of the REI human light chain have at least 69% sequence identity with the corresponding framework regions of monoclonal antibody LL2 and murine framework residues having potential CDR contacts were retained in the design of the humanized

framework sequences and framework residues within 4.5 Angstrom radius of any atoms within any CDR can be retained in the humanized LL2 monoclonal antibody (see entire document, particularly example 1 at col. 11, col. 6, lines 5-9, and Fig. 1). Leung et al [a] also teaches a method of producing the humanized LL2 monoclonal antibody comprising said designed amino acid variable domain sequences comprising preparing a DNA sequence encoding the designed amino acid variable domain sequences and operably incorporating the DNA sequences into vectors comprising the human kappa and IgG1 constant regions, introducing the vectors into Sp2/0-Ag14 cells by electroporation and culturing the cells under conditions to produce the humanized LL2 monoclonal antibody (see col. 12-16 and Figs 3 and 6).

Thus, Leung et al [a] anticipates the claims.

(10)(b) Response to Argument

Appellant states that the instant application is a continuation of USSN 09/741,843, filed 12/22/00, which is a continuation of USSN 09/127,902, filed 8/3/98 (now U.S. Patent No. 6,187,287), which is a continuation of USSN 08/690,102, filed 7/31/96 (now U.S. Patent No. 5,789,554), which is a continuation of USSN 08/289,576, filed 8/12/94. Support for the instant claimed subject matter may be found going back to the original priority document, USSN 08/289,576, filed 8/12/94, as detailed above under Section A of the Brief on Appeal. Appellants' arguments have been fully considered but are not found persuasive. As discussed above in Sections (9)(a) and (10)(a), the disclosure of the instant application does not to provide adequate written support in the manner provided by the first paragraph of 35 U.S.C. 112 for the presently claimed subject matter. Accordingly, the filing date of the instant claims is deemed to be that of the instant application, i.e., 11/16/2001 and appellants' "great grandparent" application, now US Patent 5,789,554, teaches a species that anticipates the claimed invention. See *In re Lukach,* 442 F.2d 967, 169 USPQ 795 (CCPA 1971), wherein the court held that a U.S. "grandparent" application did not sufficiently describe the later-claimed invention, but that the appellant's intervening British application, a counterpart to the

U.S. application, anticipated the claimed subject matter. As the court pointed out in *In re Lukach,* 442 F.2d 967, 169 USPQ 795 (CCPA 1971), "the description of a single embodiment of broadly claimed subject matter constitutes a description of the invention for anticipation purposes ..., whereas the same information in a specification might not alone be enough to provide a description of that invention for purposes of adequate disclosure...." *Id.* at 970, 169 USPQ at 797 (citations omitted).

For these reasons the rejection of claims 28-29 and 31-32 under 35 U.S.C. 102(b) as being anticipated by Leung et al [a] is maintained.

(9)(c) Grounds of Rejection

Claims 28-29 and 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung et al [b] (Molecular immunology, 32(17-18):1413-1427, 1995, cited on PTO-892 mailed 2/20/2004).

Leung et al [b] teach a method of designing the amino acid sequences of the variable domains of a humanized monoclonal antibody comprising comparing the murine variable domain framework sequences of monoclonal antibody LL2 to that of human antibodies in the Kabat database and selecting the human REI (VL) and human EU (VH) frameworks as the frameworks onto which the LL2 CDRs were grafted, however, the FR4 sequence of human NEWM was used in place of the human EU FR4 in the heavy chain (i.e., framework regions form at least three different human antibodies (REI, EU and NEWM) and the heavy chain framework regions are from at least two different human antibodies (EU and NEWM)) and the framework regions of the EU human heavy chain and FR4 of NEWM have at least 62.5% sequence identity with the corresponding framework regions of monoclonal antibody LL2 and the framework regions of the REI human light chain have at least 69% sequence identity with the corresponding framework regions of monoclonal antibody LL2 and murine framework residues having potential CDR contacts were retained in the design of the humanized framework sequences and framework residues within 4.5 Angstrom radius of any atoms within any CDR can be retained in the humanized LL2 monoclonal antibody (see entire

document, particularly the abstract, pp. 1414-1416 and Fig. 1). Leung et al [b] also teaches a method of producing the humanized LL2 monoclonal antibody comprising said designed amino acid variable domain sequences comprising preparing a DNA sequence encoding the designed amino acid variable domain sequences and operably incorporating the DNA sequences into vectors comprising the human kappa and IgG1 constant regions, introducing the vectors into Sp2/0-Ag14 cells by electroporation and culturing the cells under conditions to produce the humanized LL2 monoclonal antibody (see entire document, particularly pp. 1414-1418 and Figs. 3-4).

Thus, Leung et al [b] anticipates the claims.

(10)(c) Response to Argument

Appellant states that the instant application is a continuation of USSN 09/741,843, filed 12/22/00, which is a continuation of USSN 09/127,902, filed 8/3/98 (now U.S. Patent No. 6,187,287), which is a continuation of USSN 08/690,102, filed 7/31/96 (now U.S. Patent No. 5,789,554), which is a continuation of USSN 08/289,576, filed 8/12/94. Support for the instant claimed subject matter may be found going back to the original priority document, USSN 08/289,576, filed 8/12/94, as detailed above under Section A of the Brief on Appeal. Appellants' arguments have been fully considered but are not found persuasive. As discussed above in Sections (9)(a) and (10)(a), the disclosure of the instant application does not to provide adequate written support in the manner provided by the first paragraph of 35 U.S.C. 112 for the presently claimed subject matter. Accordingly, the filing date of the instant claims is deemed to be that of the instant application, i.e., 11/16/2001 and Leung et al [b] teaches a species that anticipates the claimed invention.

For these reasons the rejection of claims 28-29 and 31-32 under 35 U.S.C. 102(b) as being anticipated by Leung et al [b] is maintained

For the above reasons, it is believed that the rejections should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

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